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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/726,752	12/02/2003	Ian Richard Buxton	PU4727US-1	6812

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EXAMINER	
RAMACHANDRAN, UMAMAHESWARI	
ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
02/05/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/726,752	BUXTON ET AL.	
	Examiner	Art Unit	
	UMAMAHESWARI RAMACHANDRAN	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34,42,45 and 46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34, 42, 45, 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/14/2008 has been entered.

Claim 34 has been amended and claims 1-33, 35-41, 43, 44 have been cancelled. Claims 34, 42, 45 and 46 are currently pending and are being examined on the merits herein.

Response to Remarks

Applicants' arguments regarding the rejection of claims 33-42 under 35 U.S.C. 103(a) as being unpatentable over Nadkarni (WO 03/104192) in view of Staniforth (U.S. 5,004,614) and Jain et al. have been fully considered but are moot in view of the modified rejections presented in this office action. Applicants' amendments and further consideration necessitated the modified rejections given below. Accordingly, the office action is made non-final.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 34, 42, 45, 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nadkarni (WO 03/104192) in view of Staniforth (U.S. 5,004,614).

Nadkarni teaches controlled release formulations of lamotrigine or a pharmaceutically acceptable salt in a core to provide better control of blood plasma level (see Abstract). The core particles comprises lamotrigine and hydoxypropyl methyl cellulose and Nadkarni further teach a release rate controlling polymer such as polymers of methacyrlic acids, poly (methyl methacrylate), poly (ethyl methacrylate) etc (see Abstract, p 6, lines 30-34) in the composition as coat particles. The reference teaches the addition of excipients, diluents such as microcrystalline cellulose, lactose and lubricants such as magnesium stearate (p 9 lines 24-25, p 10, line 8). The reference also teaches Eudragit RL as a suitable polymer (p 31, lines 4-5). The reference further teaches the amount of polymer(s) to be used in forming the particles will be determined based on the amount of drug to be delivered, the drug release rate desired, and the size of the particles and the total amount of the particles including copolymer, filler, plasticizer, excipients and processing aids, are preferably in the range of 5% to 60% weight gain on the cores (p8, lines 9-15). The reference teaches that controlled release lamotrigine, which is designed to avoid excessive Cmax levels will produce lower plasma concentrations, which are reached over a longer period of time (p3, lines 6-7). Nadkarni teach the weight of lamotrigine as 51 % (900 g of lamotrigine added to provide 1750 g of controlled release particles, example 1), and the weight of release retarding polymer such as hydroxypropyl methyl cellulose to be 31% (545.5 g of the polymer added to provide 1750 g of controlled release particles, example 1). The

reference teaches the weight of microcrystalline cellulose to be 57% by weight (493.5 g added to total weight of 867.05 g, example 4) and the lubricants may comprise from 0.05 to 10 weight % of the formulation (p10, lines 1-15). The reference further teaches that the core may also include further components to those specified above such as dispersing agent, glidant and/or surfactant. Examples of glidant include magnesium stearate, talc etc. (http://en.wikipedia.org/wiki/Glidant) (p 6, lines 9-10). The specification teaches magnesium stearate as one of the lubricants. In summary, Nadkarni et al. teaches a core comprising lamotrigine, a release retarding polymer such as HPMC, compression aid/diluent such as microcrystalline cellulose, binder such as povidone, and further teaches glidants can be added and coating of the core particles with a polymer such as rate controlling polymer such as poly (methyl methacrylate), poly (ethyl methacrylate) in 5 to 60% of core particles.

The reference does not teach the thickness of outer coating or outer coating with one or more orifices.

Staniforth teach a device for controlled release of an active agent, comprising a core comprising an active agent and a release modifying agent; and an outer coating covering said core, the thickness of said coating being adapted such that it is substantially impermeable to the entrance of an environmental fluid present in an environment of use and substantially impermeable to the exit of said active agent during a dispensing period, said coating including an orifice extending substantially completely through said coating but not penetrating said core and communicating from said environment of use to said core for allowing the release of said active agent into said

environment of use, said orifice having an area from about 10 to about 60 percent of the face area of said device, the rate limiting step for the release of said active agent substantially being the exit of said active agent through said orifice via one or more of dissolution, diffusion or erosion of said active agent in solution or suspension (col.16, lines 1-24, claim 1). The reference further teaches the drug to be an active agent (col. 5, lines 54-56). The reference teaches diluents such as lactose, fructose etc (col. 5, line 4), magnesium stearate (0.25-5%) weight of the core as a lubricant (col. 5, line 19) and hydroxypropylmethyl cellulose for thick coatings of the polymeric materials (col. 6, lines 60-65). The reference teaches that the thickness of the coating necessary to provide results in accordance may be simply determined by one of ordinary skilled in the art via the preparation of devices with differing coating thicknesses, performing dissolution tests in the devices without the inclusion of an orifice in the device, and choosing the coating thickness which does not allow the release of the active agent from the device during the desired duration of controlled release (col. 7, lines 3-13). The reference further teaches that release-modifying agents may be used to slow the release of active agent from the device and examples of such agents include insoluble polymers.

It would have been obvious to one of ordinary skill in the art at the time of the invention to make a sustained release formulation of lamotrigine with an outer coat covering said core impermeable to environmental fluids because of the teachings of Nadkarni and Staniforth. Nadkarni teaches that the advantage of controlled release of a drug is to provide therapeutically effective level of an agent for an extended period of time and longer period of pharmacological and diagnostic response and teaches

sustained release formulation of lamotrigine. Staniforth teaches a different technique of controlled release formulation of drugs by adjusting the thickness of the outer coating so that it is substantially impermeable to the entrance of an environmental fluid present in an environment of use and substantially impermeable to the exit of said active agent during a dispensing period. Hence one of ordinary skill in the art would have been motivated to combine the teachings of Nadkarni with Staniforth to provide a sustained release formulation of lamotrigine with an outer coating that is impermeable to environmental fluid and impermeable to the exit of an active agent such as lamotrigine. One having ordinary skill in the art at the time of the invention would have been motivated in formulating a sustained release formulation with a core and a coat with one or more orifices for desired release of drug through one or more of the exits in the coat.

The references do not explicitly teaches that a matrix tablet in which there are two phases in the release of lamotrigine or a pharmaceutically acceptable derivative thereof, wherein the release rate in the first phase takes place in the oesophagus and stomach and is slower than the release rate in the second phase which takes place when the surrounding pH exceeds 5. However, combined teachings of Nadkarni and Staniforth teach a core comprising an outercoat with orifice comprising the same components as claimed in the instant application. Thus the pharmaceutical formulation from the combined teachings would have two release phases the release rate of the first phase taking place in the oesophagus and stomach and is slower than the release rate in the second phase which takes place when the surrounding pH exceeds 5.

The references do not explicitly teach the outer coat dissolve when the surrounding pH exceeds 5.

It would have been obvious to one of ordinary skill in the art at the time of the invention that the outer coat of sustained formulation of lamotrigine dissolves when the surrounding pH exceeds 5 because Nadkarni teach rapidly disintegrating multiparticulate controlled release formulations of lamotrigine and the rate-controlling membrane containing methacrylate copolymers, Eudragit polymers as the one taught in the specification of the instant application (para 0118) for film coating. Nadkarni teach a controlled release formulation of lamotrigine with an outer coat made of the same polymers as the instantly claimed application. The properties are inseparable from a compound and therefore, if the prior art teaches the identical chemical structure, the properties Applicant discloses and/or claims are necessarily present. Hence the outer coating of Nadkarni's sustained release formulation will inherently dissolve when the surrounding pH exceeds 5.

The reference does not teach a value for the thickness of the outer coat polymer as claimed in claim 38 of the instant application.

It would have been obvious to one of ordinary skill in the art at the time of the invention to make an outer coat of the formulation of lamotrigine with 0.05-0.30 mm of polymer. The motivation to do so is provided by Staniforth's teachings. The reference clearly teaches that the thickness of the coating necessary to provide results in accordance may be simply determined by one of ordinary skilled in the art via the preparation of devices with differing coating thicknesses, performing dissolution tests in

the devices without the inclusion of an orifice in the device, and choosing the coating thickness which does not allow the release of the active agent from the device during the desired duration of controlled release (col. 7, lines 3-13). Hence one of ordinary skill in the art would have been able to adjust the thickness of the outer coat of the sustained formulation of lamotrigine by routine experimentation as Staniforth teaches the controlled release device having a core and an outer coating and the outer coating polymer materials and examples to make the formulation.

The reference does not teach the AUC values or the Cmax values after administration of sustained release formulation of lamotrigine as in claim 42.

It would have been obvious to one of ordinary skill in the art that the sustained formulation comprising lamotrigine having a Cmax less than the instant release tablet containing the same amount of lamotrigine because Nadkarni teaches that the controlled release lamotrigine, which is designed to avoid excessive Cmax levels will produce lower plasma concentrations, which are reached over a longer period of time. Also, it is obvious to one of ordinary skill in the art that the sustained release formulation comprising the same composition taught by the teachings of Nadkarni and Staniforth will have same release profile and the properties such as AUC and Cmax values.

Response to Arguments

Applicants' argue that Nadkarni's multiparticulate formulation is not formulated like Applicants and In Nadkarni, lamotrigine and excipient(s) are made to form discrete core particles, each of which is then layered with one or more different rate controlling polymers or membranes (Nadkarni, claim 2). Preferably the core particle is built around

inert nuclei or bases (e.g., sugar) (Nadkarni, page 6, lines 2-10). In response, the claim of the instant application is directed to a sustained-release composition comprising a core and an outer coat, core comprising lamotrigine, a release retarding polymer, lubricant, diluent, compression aid and an outer coat comprising 0.05 mm to 0.30 mm of polymer. Nadkarni as cited above teaches a sustained release formulation comprising a core and an outer coat. The core particles comprising lamotrigine, a release retarding polymer such as HPMC, compression aid/diluent such as microcrystalline cellulose, binder such as povidone, and further teaches glidants can be added and coating of the core particles with a polymer such as rate controlling polymer such as poly (methyl methacrylate), poly (ethyl methacrylate). The reference does not teach exits or orifices in the outer coat. However, it is well known in the prior art (Staniforth) to formulate sustained release formulations comprise a core and a coat with one or more orifices for desired rate of release of the drug. Hence one having ordinary skill in the art would have been motivated to add an exit or an orifice in the outercoat of the Nadkarni's formulation for desired rate of release of the active drug. The reference does not explicitly teach the thickness of the outercoat . However Staniforth teaches that thickness of the coating necessary to provide results in accordance may be simply determined by one of ordinary skilled in the art. One of ordinary skill in the art would have been able to adjust the thickness of the outer coat of the sustained formulation of lamotrigine by routine experimentation. The claims of the instant application has a comprising language and does not exclude forming discrete core particles or core particle built around sugar. Accordingly, the combined references of Nadkarni and Staniforth teaches the instantly

claimed formulation of a core comprising lamotrigine, release retarding polymers, lubricants etc, and an outercoat comprising a polymer and an outercoat with orifices.

Applicants' argue that neither Staniforth nor Nadkarni provide a system wherein the lamotrigine active is released in two phases, the first phase having a slower release than the second and nor does the combination of the teachings achieve a slower first phase of release than the second. In response, as stated above, combined teachings of Nadkarni teach a sustained release formulation comprising a core particles comprising lamotrigine, a release retarding polymer such as HPMC, compression aid/diluent, binder etc and coating of the core particles with a polymer such as rate controlling polymers and Staniforth's teachings provide a motivation to add orifices to the outercoat. Thus the combined teachings of Nadkarni and Staniforth teach a core comprising an outercoat with orifice comprising the same components as claimed in the instant application. Thus the pharmaceutical formulation from the combined teachings would have two release phases the release rate of the first phase taking place in the oesophagus and stomach and is slower than the release rate in the second phase which takes place when the surrounding pH exceeds 5 as claimed in the instant application.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to UMAMAHESWARI RAMACHANDRAN whose telephone number is (571)272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SREENI PADMANABHAN/
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